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Integrated Roles of Glucoregulatory Hormones during Postprandial, Postabsorptive, and Stress States of Metabolism: A Review

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Introduction

Blood glucose homeostasis is the process by which glucose levels are maintained and regulated in the blood (euglycemia) by a tightly integrated system of various hormones and neuropeptides released mainly from the pancreas, liver, intestine, muscle tissue, adipose tissue, and brain. Disturbance in the interplay of these hormones and peptides may cause metabolic disorders such as diabetes mellitus (DM).

DM is a chronic disease that occurs when the pancreas cannot produce enough insulin (insulin deficiency) or the body cannot effectively utilize insulin (insulin resistance), or there is a combination of deficient insulin secretion and insulin resistance, which results in high glucose plasma level (hyperglycemia) causing tissue damage over time.[1-4] There are two common types of DM that account for the majority of cases: type 1 and type.[2] In type 2 DM, this dysfunction is attributed to decreased insulin secretion and marked insulin resistance, resulting in abnormal glucose homeostasis that ultimately causes detrimental macrovascular and microvascular effects. DM has widespread implications both clinically and financially. DM is also the major risk factor for heart disease and stroke, the first and fifth leading causes of death, respectively.[5,6] The epidemic of DM also has considerable financial impacts with total annual medical costs estimated at $245 billion as of 2012.[7] As a result, it is imperative to understand fully the underlying pathophysiology of DM, specifically glucose homeostasis and its regulation.

This review focuses on the roles of the main regulatory and counter-regulatory hormones that are involved in the physiological regulation of blood glucose. These hormones either stimulate or suppress key metabolic enzymes during the various stages of metabolism. Previous review articles have described

the physiology of glucose homeostasis, but they have not detailed the interplay between the regulatory hormones and metabolic enzymes during the various stages of metabolism.[8-11] In addition, the roles of additional key glucoregulatory hormones believed to be involved in glucose homeostasis, namely amylin and irisin, have also not been previously reviewed. That are important to note, however, that while many hormones may dramatically increase in concentration during a particular phase, all hormones exist in detectable concentrations in circulation at all times, and it is the integrated balance of those hormone levels that determines glucose homeostasis.

Glucose in Circulation

Blood glucose levels fluctuate within a relatively narrow window throughout the day. The average value during a 24-hour period is approximately 90 mg/dl, with a maximum of about 165 mg/dl after a meal, and typically no less than 55 mg/dl during a fast or after exercise.[12-14] Blood glucose homeostasis is maintained

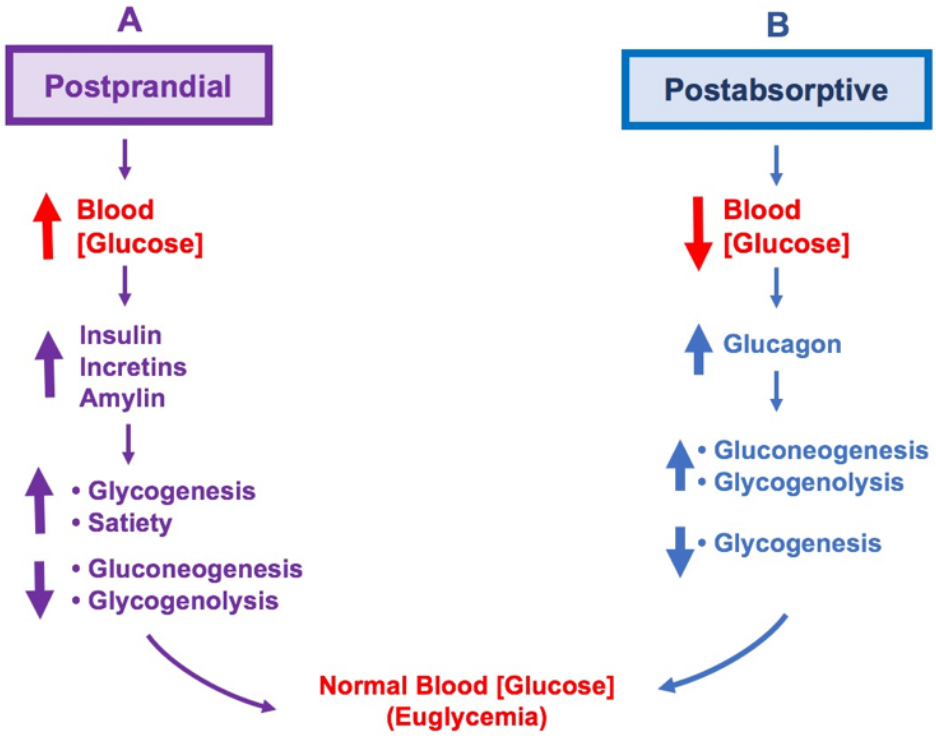

Figure 1. Postprandial State.
Hormonal and metabolic changes during the postprandial (fed) phase (A) and postabsorptive phase (B). Changes in blood glucose following fed (postprandial) and postabsorptive states lead to a sequelae of hormonal and metabolic changes that ultimately function to restore euglycemia.

through integration of the neuro-hormonal system. This review focuses on the interaction between different endocrine hormones, which play the major role in regulating blood glucose homeostasis. Increases in blood glucose levels will stimulate the release of various hormones (mainly insulin and amylin) that promote glucose cellular uptake and inhibit hepatic cellular release of glucose, whereas decreases in blood glucose levels will stimulate the release of other hormones (glucagon, catecholamines, growth hormone, and cortisol) that suppress the release of insulin and stimulate the production and release of glucose into circulation, thus restoring euglycemia.[15,16]

The blood glucose comes from three different sources: 1) dietary or exogenously ingested glucose; 2) glycogenolysis, which is releasing of endogenous glucose from the breakdown of glycogen storage in liver; and 3) gluconeogenesis, which is the formation of endogenous glucose in the liver and kidney from substrates such as lactate, pyruvate, amino acids, and glycerol. The relative amount of blood glucose attributed from these sources depends on the time since the last meal. The period following a meal is known as the postprandial or fed, state and it is characterized by elevated blood glucose levels and a release of insulin and other regulatory hormones. In contrast, the postabsorptive, or fasting, state occurs about six hours after the last meal, and it is characterized by relatively lower levels of blood glucose and the release of glucagon, catecholamines, and other regulatory hormones. There are additional metabolic states that are associated with the release of other regulatory hormones based on specific requirements, including periods of stress due to rigorous exercise or trauma, and prolonged fasting.[15-17]

Postprandial State (Fig. 1.)

Following a meal, dietary glucose accumulates in the plasma and blood glucose values reach a maximal concentration usually not exceeding 165 mg/dl after ingestion, resulting in the fed state.[13] This increase in plasma glucose stimulates the release of various hormonal regulators, insulin and amylin, and it suppresses the secretion of various others, largely glucagon. Complete absorption of the constituents of a mixed meal containing fat, protein, and carbohydrate and restoration of the postabsorptive state take about six hours.[13] In a typical day in which an individual consumes three meals, the majority of the day is spent in the postprandial state.

Dietary glucose taken up by tissues in the postprandial state has various fates. Upon insulin secretion, glucose is taken up mostly by muscle and fat cells to undergo glycolysis (~66%), or to be immediately stored in the liver as glycogen via glycogenesis. Of the glucose undergoing glycolysis, two thirds will be oxidized, yielding energy in the form of ATP; the remainder will undergo non-oxidative glycolysis, which leads to to the formation of three carbon compounds: pyruvate, lactate, and alanine. These compounds will then undergo gluconeogenesis in liver to reproduce glucose, and they will either be stored as glycogen via the indirect pathway or be released into plasma.[18] The major factors regulating postprandial glucose homeostasis are those that affect

the suppression of endogenous glucose release and those that affect tissue glucose uptake.

Insulin

β cells in the pancreatic islets produce, store, and release insulin in response to increases in blood glucose concentration. Increased blood glucose in the postprandial state results in a three- to four-fold increase in plasma insulin within 30–60 minutes (~40–50 μU/ml). Acute increases in amino acids, and to a lesser extent, FFA also increase insulin secretion.[8,16] Insulin regulates glucose metabolism through binding to its receptors in the liver, kidney, muscle, and adipose tissue. Insulin thus activates its signaling pathway, which involves a complex cascade of protein kinases and regulatory proteins, and induces several effects: the translocation of glucose transporters in muscle, and adipose tissue to increase their glucose uptake;[19] the inhibition of glucose release from liver and kidney;[20] and the inhibition of free fatty acid release into circulation.[21]

The influx of glucose into cells requires specific transporter proteins to facilitate its diffusion across the cell membrane. This is due to its hydrophilic nature and relatively slow diffusion rate across the hydrophobic cell membrane. The regulatory role of insulin in blood glucose homeostasis is largely dependent on its ability to promote the synthesis and mobilization of these glucose transporters to the cell membrane.[19,22] There are currently two known families of glucose transport proteins: facilitative glucose carriers (GLUTs) and sodium-glucose cotransporters (SGLTs). Among the GLUTs, GLUT4 mediates insulin-stimulated glucose uptake into skeletal muscle, heart, and white and brown adipose tissues. Insulin increases the cell surface expression levels of GLUT4 by increasing the rate of externalization and reducing the rate of internalization. Thus, during the postprandial state and conditions of high insulin levels, there is increased glucose entry into muscle and into adipose cells due to the greater number of GLUT4s at the cellular membrane.[23,24] GLUT2 enables facilitated glucose transport across the cellular membranes of the liver and pancreatic β cells, though unlike GLUT4, it does not rely on insulin for facilitated diffusion.[24] SGLTs are also insulin-independent and utilize an electrochemical sodium gradient to transport glucose against its concentration, and they are primarily responsible for the uptake of dietary glucose from the small intestine lumen.[23,25]

In addition to reducing blood glucose levels via increased cellular uptake, insulin suppresses glucose release from the liver and kidneys. The effect of insulin on the liver is to suppress the release of glucose into circulation by inhibiting hepatic glucose-producing and releasing pathways (glycogenolysis and gluconeogenesis) as well as by promoting the accumulation of glucose storage into hepatic glycogen (glycogenesis). This is accomplished through insulin's inhibitory effect on glucose-6-phosphatase and glycogen phosphorylase, enzymes involved in the gluconeogenesis and glycogenolysis pathways, respectively, while also stimulating glycogen synthase.[8,20] Furthermore, the effect of insulin on

renal glucose release is largely attributable to the suppression of renal gluconeogenesis, and ultimately to the suppression of renal glucose release. This is because, unlike the liver, renal glycogen stores are negligible. It is thought that insulin-suppressed renal gluconeogenesis is accomplished by decreasing the supply of gluconeogenic precursors and inhibiting gluconeogenic enzymes, and/or by stimulation of alternate pathways for disposal of potential gluconeogenic precursors.[20]

Lastly, insulin has an inhibitory effect on the release of free fatty acids (FFA) into circulation from stored triglycerides within adipose tissue due to suppression of hormone-sensitive lipase and a simultaneous increase in FFA clearance from the circulation.[21] Research has shown that FFA stimulate gluconeogenesis and reduce glucose uptake into cells. Thus, the inhibitory effect of insulin on FFA release indirectly promotes glucose uptake and reduces blood glucose levels.[21,26]

Incretins

In the postprandial state, intestinal factors that are called incretins, GLP-1 (glucagon-like peptide) and GIP (gastrointestinal-inhibitory peptide), regulate the secretion of insulin and other hormones. These factors are secreted from the intestinal endocrine mucosa (L and K cells) in response to nutrient ingestion, and they subsequently stimulate the pancreas to release insulin.[27] Incretins are responsible for half of the insulin released after oral glucose consumption, and they explain why plasma insulin levels increase to a greater extent after oral glucose consumption rather than after intravenous glucose, despite identical plasma glucose concentrations.[18,27,28] Both factors have been shown to suppress glucagon concentrations by inhibiting its secretion. In addition to suppressing glucagon concentrations, research has shown that GLP-1 not only stimulates insulin secretion but also decelerates gastric emptying, which promotes satiety and decreases food intake, possibly through neural mechanisms.[29] There has been increasing interest in the therapeutic potential of GLP-1 due to its regulatory effects on hormones and its association with weight loss.[27]

Amylin

Amylin (also known as islet amyloid polypeptide [IAPP]) is a pancreatic β-cell hormone whose secretion correlates very tightly with insulin secretion and produces effects in several different organ systems, including the brainstem. Amylin is co-secreted with insulin in a fixed molecular ratio of approximately 20:1 (insulin: amylin).[30-32] Similar to insulin, amylin can be stimulated by many factors, including glucose, arginine, and fatty acids. Additionally, the incretin, glucagon-like peptide 1 (GLP-1), can increase plasma amylin concentrations in healthy subjects. Amylin activates its specific G protein–coupled receptors and has a major role as a glucoregulatory hormone by inhibiting postprandial glucagon secretion.[33-35]

Recently, amylin has been extensively investigated in its role as a signal of satiation and adiposity.[36] It is thought that amylin is a physiologic regulator of meal size via neural mechanisms. Eating leads to a rapid increase in circulating amylin

levels, and it has been shown that exogenous amylin administration reduces eating within minutes after administration, offering a potential future therapeutic option for obesity. These actions are mediated through amylin action in the brainstem, where several areas are shown to carry high-affinity binding sites. Amylin concentrations may also serve as an index of the degree of adiposity in the body because blood concentrations of amylin are increased in adiposity.[36,37]

Amylin is an important regulator of nutrient metabolism and utilization because it reduces energy intake in its role as a signal of satiation, and it increases energy disposal by preventing compensatory decreases of energy expenditure in weight-reduced individuals. The mechanisms involved in amylin's effect on energy expenditure, however, are much less known.[34,38] Pramlintide is a synthetic analog of amylin that is used as an adjunct therapy to mealtime insulin in the treatment of diabetes mellitus.[39]

Somatostatin

Somatostatin is a peptide hormone produced by the brain, the gut, and Δ cells of the pancreas, and it is frequently described as an inhibitory hormone. Somatostatin is released in response to increased levels of blood glucose and it functions as a potent inhibitor of insulin and glucagon secretion from the pancreas.[40] The five distinct somatostatin receptors are all inhibitory Gi/o-protein coupled receptors, and activation inhibits adenylate cyclase activity, thereby reducing cAMP levels and protein kinase A-stimulated secretions. As a result of the mass inhibition of glycogen synthase, glucose-6-phosphatase, and glycogen phosphorylase, somatostatin has no direct role in the increase or reduction of glucose; and rather it serves as a regulator of the endocrine system.[40,41]

Irisin

Irisin was first described in 2012 as a hormone secreted from muscle cells and adipose tissue during exercise to increase energy expenditure.[42] Although the mechanisms surrounding the regulation and precise role of irisin remain unclear, recent studies have revealed its role in glucose homeostasis. One of the main targets of irisin is adipose tissue, where it stimulates the conversion of white fat to brown fat, or the "browning" of adipose tissue by augmenting gene expression.[42,43] In contrast to white adipose tissue, brown adipose tissue has ten times more insulin-mediated glucose uptake, ultimately increasing energy expenditure and decreasing blood glucose levels.[44] The increase in glucose uptake results from the upregulation of GLUT4 expression seen in adipose tissue and human skeletal muscle.[44-46] Additionally, in the liver, the administration of irisin has been shown to reduce gluconeogenesis and stimulate glycogenesis through the activation of glycogen synthase, further contributing to irisin's role in reducing blood glucose levels and restoring euglycemia.[47]

The Postabsorptive State (Fig 1.)

After about 6 hours of fasting, plasma glucose concentrations remain relatively stable within a narrow range of 70-100 mg/dl. During this period, or the postabsorptive state, the rate of glucose released into circulation (equally via

glycogenolysis and gluconeogenesis) equals the rate of glucose removed from circulation.[16] The rate of glycogenolysis depends on the opposing activities of glycogen synthase and glycogen phosphorylase, and gluconeogenesis is regulated by the activity states of fructose-1,6-diphosphatase, phosphoenolpyruvate carboxylkinase, and pyruvate dehydrogenase.[16] The activities of these enzymes are largely dependent on their stimulation or suppression by hormonal regulators.

Glucagon

Glucagon is a hormone secreted from the pancreatic α cells and it is the major counterpart to insulin in the regulation of blood glucose. The main factors that control the release of glucagon are direct effects of glucose and insulin, though neural signals, zinc, FFA, and amino acids play a limited role. The glucoregulatory role of glucagon is to increase blood glucose levels through the stimulation of hepatic glycogenolysis in response to hypoglycemia in the postabsorptive state.[40,48] Glucagon acts exclusively on the liver, where it binds to glucagon receptors and activates adenylate cyclase. As a result, intracellular cAMP increases, which stimulates glycogen phosphorylase, and glycogenolysis occurs.[49,50] During the early periods of the postabsorptive state, hepatic glucose output via glycogenolysis is responsible for approximately 80% of glucose release into the circulation.[16,40]

Stress

Under stressful conditions (i.e., exercise, trauma) and/or increased sympathetic nervous system tone the release of other hormones, such as catecholamines, growth hormone, and cortisol, has significant glucoregulatory roles. Essentially, their actions are to increase the availability of glucose by increasing renal gluconeogenesis and hepatic gluconeogenesis and glycogenolysis.[14,16,48,51] The regulatory roles of these factors are similar to glucagon and they can be summarized as being antagonistic to the action of insulin; they reduce the ability of insulin to promote glucose uptake from circulation, inhibit hepatic and renal glucose production and release, and inhibit lipolysis. While the effects of glucagon and catecholamines are evident almost immediately, the metabolic actions of growth hormone and cortisol typically take several hours.[51-54]

Catecholamines

Catecholamines (epinephrine and norepinephrine) are hormones derived from the amino acid tyrosine, and they are released from the adrenal medulla of the adrenal glands.[55] Their release is mediated through changes in the sympathetic nervous system, being increased during states of stress and hypoglycemia. Catecholamines inhibit insulin secretion and, like glucagon, effectively increase blood glucose levels.[51,53,56]

Catecholamine actions at the liver are mediated via direct agonism of the hepatic 2 adrenergic receptors. Catecholamine binding of these receptors stimulates the activity of adenylyl cyclase, causing an increase in intracellular cAMP levels and subsequent activation of glycogen phosphorylase. As a result, the liver directly undergoes increased glycogenolysis, and indirectly gluconeogenesis, through increasing

gluconeogenic substrate availability, particularly lactate, and plasma FFA.[48,53] The release of lactate is due to catecholamine reduction of glucose uptake and stimulation of glycogenolysis in skeletal muscles. In adipose tissue, catecholamines stimulate lipolysis by activating hormone-sensitive lipase, which hydrolyzes stored triglycerides and causes a release of FFA and glycerol, which are other key gluconeogenic precursors.[10,51,53,57] In the kidneys, catecholamines are potent stimulators of gluconeogenesis directly by activating gluconeogenic enzymes, and indirectly by increasing substrate availability.[51]

Growth Hormone

Human growth hormone (hGH) is a hormone secreted by the anterior pituitary gland. It acts through binding to the hGH receptor, inducing direct and indirect effects to promote growth in children and adolescents.[58] Additionally, hGH has

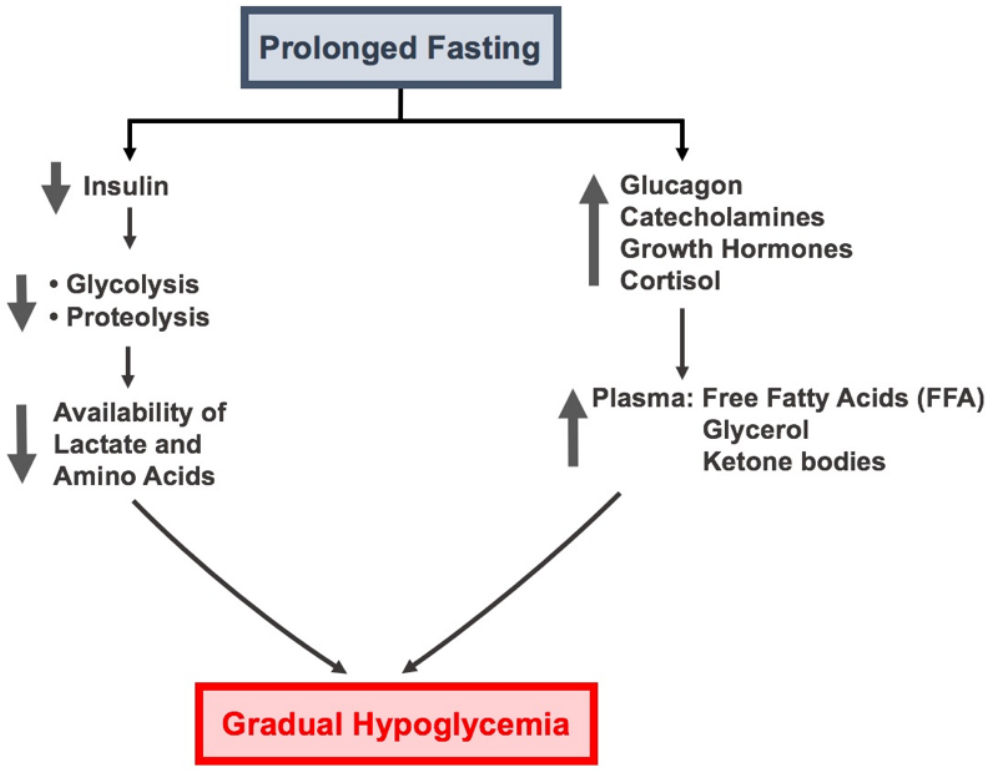

Figure 2. Hormonal and metabolic responses following prolonged fasting.
Hormonal changes in response to prolonged fasting function to increase availability of gluconeogenic precursors and ultimately glucose release into circulation. As fasting continues, essential substrates, such as lactate and amino acids are limited. These change result in gradual hypoglycemia which is typically seen during prolonged fasting (>60 hours).

various important metabolic functions throughout adult life; its regulatory role in blood glucose homeostasis has been described.[21,26,59] Growth hormone increases blood glucose levels, like glucagon, via being antagonistic to insulin. It has been shown that growth hormone directly increases gluconeogenesis by stimulating glucose-6-phosphatase, and indirectly by increasing FFA release, due to activation of hormone-sensitive lipase.[59] As described earlier, lipolysis results in the release of FFA, a gluconeogenic precursor, and as a result, stimulates gluconeogenesis.[21,26]

Cortisol

Cortisol is a glucocorticoid hormone produced in the adrenal cortex of the adrenal glands, and is released in response to stress and low blood glucose concentrations. Like hGH and glucagon, the actions of cortisol counteract those of insulin and effectively increase plasma glucose levels. Cortisol increases gluconeogenesis by stimulating gluconeogenic enzymes and reduces peripheral glucose uptake. Additionally, cortisol indirectly increases gluconeogenesis by accelerating lipolysis.[52,60] Elevated plasma cortisol concentrations have been shown to impair insulin secretion, and they have been implicated in the mechanism of insulin-resistance during immunosuppressive glucocorticoid treatment.[60,61]

Prolonged Fasting

After about 24 hours of fasting and continuous glycogenolysis, hepatic glycogen stores begin to exhaust, and gluconeogenesis, both hepatic and renal, becomes the dominant pathway for glucose release into circulation. This increase in gluconeogenesis is due to increased uptake of gluconeogenic precursors, namely lactate.[40,51,62]
At about 60 hours of prolonged fasting, there is a decrease in glucose release as both hepatic and renal gluconeogenesis decreases (Fig 2).[63]

Conclusion

This review summarizes the hormonal regulation of blood glucose during the various stages of metabolism, namely during the postprandial and postabsorptive stages, stress, and prolonged fasting. It highlights the complex and sophisticated mechanisms by which the body's hormones constantly fluctuate and interact to maintain glucose homeostasis (euglycemia), by activating and suppressing metabolic enzymes. It is important to understand the interactivity of such key regulatory hormones, such that dysregulation of these mechanisms are common and lead to deleterious consequences, such as those seen in DM. By examining the key regulatory hormones that are intimately involved in these processes, advancements in pharmacological treatments of DM can improve.

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